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10/761,208	01/22/2004	Masatoshi Narahara	HIRA.0136	3740

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REED SMITH LLP
Suite 1400
3110 Fairview Park Drive
Falls Chuch, VA 22042

EXAMINER	
CROW, ROBERT THOMAS	
ART UNIT	PAPER NUMBER
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/761,208	NARAHARA ET AL.	
	Examiner	Art Unit	
	Robert T. Crow	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4* is/are pending in the application.

4a) Of the above claim(s) *4* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. This action is in response to papers filed 6 December 2006 in which claims 1-3 were amended, no claims were canceled, and new claim 4 was added. All of the amendments have been thoroughly reviewed and entered.

The previous rejections under 35 U.S.C. 112, second paragraph, are withdrawn in view of the amendments.

The previous rejections under 35 U.S.C. 102(b) and 35 U.S.C. 103(a) not reiterated below are withdrawn in view of the amendments. Applicant's arguments filed 25 August 2006 (i.e., the "Remarks") have been thoroughly reviewed and are addressed following the rejections necessitated by the amendments.

2. Newly submitted claim 4 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the invention of claims 1-3 and the invention of claim 4 are directed to related processes. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have materially different modes of operation and functions. The invention of claims 1-3 operates by attaching nucleic acids to maleimide coated surfaces followed by hydrolysis of unreacted maleimide groups and functions to attach nucleic acids to a surface. In contrast, the invention of claim 4 operates by hybridizing nucleic acids to an array and functions to detect nucleic acids by hybridization. Furthermore, the inventions as claimed do not encompass.overlapping subject matter and there is nothing of record to show them to be obvious variants.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 4 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

3. Claims 1-3 are under prosecution.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Chrisey et al (U.S. Patent No. 5,688,642, issued 18 November 1997 as evidenced by Okinaka et al (U.S. Patent No. 5,155,190, issued 13 October 1992). The rejection of claim 3 is a new rejection.

Regarding claims 1-3, Chrisey et al teach a method of attaching an array of single-stranded nucleic acid probes. In a single exemplary embodiment, Chrisey et al teach Example 9 (columns 14-15). In Example 9, Chrisey et al teach providing a substrate in the form of a fused silica slide that is treated with the maleimide crosslinker SMPB to form maleimide functional groups on the surface of the substrate (column 15, lines 5-20). Thiolated single stranded DNA is then covalently bound to the maleimide functional groups through a thioether linkage (i.e., claim 2; column 15, lines 5-20 and Figure 3). A binding site is the first area.

Chrisey et al further teach the slide comprises DNA that is non-covalently bound to the surface (column 15, lines 22-26). An area having the non-covalently bound DNA is the second area. Chrisey et al

further teach the slides are treated for 24 hours with a buffer at pH 7.6 to remove the non-covalently bound DNA (column 15, lines 22-26).

Page 8 of the instant specification teaches that hydrolysis of the maleimide functional groups renders them negatively charged, and that the hydrolysis is preferably performed in a pH range of 6.0 to 8.0. Thus, the treatment step of Chrisey et al results in hydrolysis of the maleimide functional groups and renders them negatively charged, and the claim has been given the broadest reasonable interpretation consistent with the specification (*In re Hyatt*, 211 F.3d1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000) (see MPEP 2111 [R-1]).

In addition, Okinaka et al teach maleimides are rapidly hydrolyzed in alkaline pH (i.e., above 7.0), and further teaches hydrolysis "hardly takes place" between pH 5.5 and pH 7.5 (column 6, lines 15-30). The passage therefore interpreted that at least some hydrolysis takes place at pH 7.5, and that hydrolysis occurs more readily above pH 7.5; namely, pH 7.6 as taught by Chrisey et al.

Thus, the prior art of Chrisey et al discloses subject matter which there is reason to believe includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not posses characteristic relied on" (205 USPQ 594, second column, first full paragraph). The treatment of the slides with a buffer at the alkaline pH of 7.6 (i.e., claim 3) for 24 hours results in hydrolysis of maleimide groups in the second area to form new functional groups that are negatively charged. Chrisey et al therefore anticipate each and every element of claims 1-3.

Response to Arguments

A. Applicant argues on pages 4-5 of the Remarks that the hydrolysis of maleimides functional groups is superior to the blocking agents of the prior art. However, Applicant's arguments fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a

patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references.

B. Applicant argues on pages 5-6 of the Remarks that Chrisey et al do not teach they hydrolysis of unreacted maleimide groups on the surface, and that Example 9 of Chrisey et al does not address the region where the nucleic acid is not bound

However, as stated above, Example 9 of Chrisey et al anticipates each and every element of the claim, as evidenced by Okinaka and in accordance with the teachings of the specification. The attachment method of Chrisey et al results in two areas on the substrate; a first area wherein a thiolated single stranded nucleic acid is **covalently** bound to the maleimide functional groups through a thioether linkage and a second area that comprises **non-covalently** bound DNA (column 15, lines 5-26 and Figure 3). Chrisey et al further teach the slides are treated for 24 hours with a buffer at pH 7.6 to remove the non-covalently bound DNA (column 15, lines 22-26). The treatment of the entire slide includes treatment of the areas where no probe is covalently bound.

As further stated above, page 8 of the instant specification teaches that hydrolysis of the maleimide functional groups renders them negatively charges, and that the hydrolysis is preferably performed in a pH range of 6.0 to 8.0.

In addition, Okinaka et al teach maleimides are rapidly hydrolyzed in alkaline pH (i.e., above 7.0), and further teaches hydrolysis "hardly takes place" between pH 5.5 and pH 7.5 (column 6, lines 15-30). The passage therefore interpreted that at least some hydrolysis takes place at pH 7.5, and that hydrolysis occurs more readily above pH 7.5; namely, pH 7.6 as taught by Chrisey et al.

Thus, the prior art of Chrisey et al discloses subject matter which there is reason to believe includes functions that are newly cited or is identical to a product instantly claimed. The treatment of the slides with a buffer at the alkaline pH of 7.6 (i.e., claim 3) for 24 hours results in hydrolysis of maleimide groups in the second area to form new functional groups that are negatively charged. Chrisey et al therefore anticipate each and every element of claims 1-3.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koster et al (U.S. Patent No. 6,133,436, issued 17 October 2000) in view of Siiman et al (U.S. Patent No. 5,945,293, issued 31 August 1998) as evidenced by Okinaka et al (U.S. Patent No. 5,155,190, issued 13 October 1992). The teachings of Okinaka et al are solely relied upon as evidence of hydrolysis of unreacted maleimides at pH 7.2.

Regarding claims 1-3, Koster et al teach a method of attaching an array of single-stranded nucleic acid probes. In a single exemplary embodiment, Koster et al teach providing beads linked to a solid support (Abstract), wherein the beads are the surface. Koster et al also teach 4-(N)-maleimidomethyl) cyclohexane-1-carboxylate (SMCC) is used as a crosslinking agent on the surface of the bead (column 5, lines 5-20), which creates maleimide functional groups on the surface. Koster et al also teach immobilizing single stranded thiolated nucleic acid probes for hybridizing to the nucleic acids on a first region of the surface covalently through a thioether (i.e., claim 2; Abstract and column 4, lines 56-65). An area wherein a nucleic acid is immobilized is the first area.

Koster et al teach chemical conversion of unreacted crosslinking moieties on the surface of the beads (e.g., Example 1). An unreacted area is the second area. Koster et al are silent to hydrolyzing the maleimide groups.

However, Siiman et al teach a method comprising the use of beads for immobilizing biological molecules having pendant maleimidyl groups for conjugation to thiol containing groups; namely, coated particles are used for immobilizing biological molecules having sulfhydryl groups (column 22, lines 59-65). Siiman et al further teach unreacted maleimidyl groups are treated with a blocking PBS buffer (column 23, lines 49-53); PBS buffer is defined as an aqueous solution having an alkaline pH of 7.2 (i.e., claim 3; column 16, lines 23-27). Siiman et al also teach the treatment has the added advantage of resulting in the blocking of unreacted functional groups (column 10, lines 61-63), which prevents unwanted side-reactions.

As noted above, page 8 of the instant specification teaches that hydrolysis of the maleimide functional groups renders them negatively charges, and that the hydrolysis is preferably performed in a pH range of 6.0 to 8.0. This treatment step is specifically for the region where there is no probe bound. Thus, the treatment step of Siiman et al results in hydrolysis of the maleimide functional groups in the area where no probe is bound and renders them negatively charged, and the claim has been given the broadest reasonable interpretation consistent with the specification.

In addition, Okinaka et al teach maleimides are rapidly hydrolyzed in alkaline pH (i.e., above 7.0), and further teaches hydrolysis "hardly takes place" between pH 5.5 and pH 7.5 (column 6, lines 15-30). The passage therefore interpreted that at least some hydrolysis takes place at pH 7.2 as taught by Siiman et al.

Thus, the prior art of Siiman et al discloses subject matter which there is reason to believe includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to prove that subject matter shown to be in the prior art does not posses characteristic relied on. The treatment of the slides with a blocking buffer at the alkaline pH of 7.2

(i.e., claim 3) results in hydrolysis of at least some maleimide groups in the second area to form new functional groups that are negatively charged. Siiman et al therefore teach the hydrolysis of at least some maleimide groups.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method as taught by Koster et al with the hydrolysis of Siiman et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted a method having the added advantage of having blocked any unreacted functional groups on the surface of the array, and thereby preventing unwanted side reactions, as taught by Siiman et al (column 10, lines 61-63).

Response to Arguments

A. Applicant's arguments on page 7 of the Remarks regarding the rejection of claim 3 under 35 USC 103(a) as obvious over Chrisey et al in view of Okinaka et al is moot in view of the withdrawn rejection.

B. Applicant argues on page 8 of the Remarks that the blocking step of Siiman et al does not result in the hydrolysis of unreacted maleimide groups in a second region, and that there is no motivation to combine the teachings.

However, as stated above, Siiman et al further unreacted maleimidyl groups are treated with a blocking PBS buffer (column 23, lines 49-53); PBS buffer is defined as an aqueous solution having an alkaline pH of 7.2 (i.e., claim 3; column 16, lines 23-27). Siiman et al also teach the treatment has the added advantage of resulting in the blocking of unreacted functional groups (column 10, lines 61-63), which prevents unwanted side-reactions.

As noted above, page 8 of the instant specification teaches that hydrolysis of the maleimide functional groups renders them negatively charges, and that the hydrolysis is preferably performed in a pH range of 6.0 to 8.0. Thus, the treatment step of Siiman et al results in hydrolysis of the maleimide

functional groups in the area where no probe is bound and renders them negatively charged, and the claim has been given the broadest reasonable interpretation consistent with the specification.

In addition, Okinaka et al teach maleimides are rapidly hydrolyzed in alkaline pH (i.e., above 7.0), and further teaches hydrolysis "hardly takes place" between pH 5.5 and pH 7.5 (column 6, lines 15-30). The passage therefore interpreted that at least some hydrolysis takes place at pH 7.2 as taught by Siiman et al.

Thus, the treatment of the slides with a blocking buffer at the alkaline pH of 7.2 (i.e., claim 3) results in hydrolysis of at least some maleimide groups in the second area to form new functional groups that are negatively charged. Siiman et al therefore teach the hydrolysis of the maleimide functional groups in the area where no probe is bound which renders them negatively charged.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Siiman et al also teach the treatment has the added advantage of resulting in the blocking of unreacted functional groups (column 10, lines 61-63), which prevents unwanted side-reactions on the array.

Conclusion

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert T. Crow whose telephone number is (571) 272-1113. The examiner can normally be reached on Monday through Friday from 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Robert T. Crow
Examiner
Art Unit 1634

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER